Remarks

The Office Action dated December 30, 2009 has been received and carefully reviewed. The following remarks form a full and complete response thereto. Claims 1- 49 have been cancelled without prejudice. Claims 50-98 are pending in the application. Claims 56, 57 and 70-98 are withdrawn from further consideration pursuant to restriction requirement. Claims 50-55 and 58-69 are currently under examination. No claims have been amended and no new matter has been added. Reconsideration of all outstanding rejections and objections is respectfully requested in view of the following remarks.

Rejection under 35 U.S.C. § 102

Claims 50, 52 and 53 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Sasaki *et al.*, Eur. J. Immunol., Vol. 27, pgs. 3121-3129, 1997) (Sasaki).

Sasaki. describes mannan-coated N-t-butyl-N'-tetradecyl-3-tetradecylamino-propion-amidine (diC14-amidine) as an adjuvant for a DNA vaccine encoding glycoprotein 160 of human immunodeficiency virus type-1 (HIV-1). In the paragraph bridging the left and right-hand columns on page 3128 of the document, it is hypothesised by the authors that the mixture forms complexes representing "small granules with mannan occupying the surface and both DNA plasmids and cationic amphiphiles [within] the core region".

In response, Applicants respectfully submit that Sasaki. does *not* disclose "a compound comprising a conjugate of a polynucleotide or oligonucleotide molecule and a carrier comprising *at least one aldehyde group*" as required by present claim 50 as there is absolutely no indication that the mannan described in Sasaki *et al.* is oxidised during its preparation such that it would contain at least one aldehyde group (see page 3122, left column under the heading "2.2 Preparation of mannan-coated diC14-amidine"). In contrast, the present specification describes that *oxidised* mannan contains at least one aldehyde group (see, for example, page 3 line 30 to page 4 line 6), and that mannan may be oxidised by treatment with sodium periodate. In this regard, it is also worth noting that the Examiner has not specifically stated that the mannan

carrier of Sasaki *et al.* contains at least one aldehyde group and, further, concedes on page 4 of the Office Action that "Sasaki *et al.* do[es] not teach [that] the carrier comprises a plurality of aldehyde groups".

Therefore, since Sasaki neither discloses that the diC14-amidine carrier bears an aldehyde group nor suggests any oxidation of said carrier, Applicant believes that the cited document does *not* anticipate the invention of present claim 50. Accordingly, it follows that Sasaki does not anticipate the invention of the dependent claims 52 and 53.

Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 50, 52-55, 59-69 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Sasaki. as relied upon above and in further view of Apostolopoulos *et al., Eur. J. Immunol.* 2000 of record cited in the IDS filed 3/7/2008 (Apostolopoulos), Liu *et al.*, *Vaccine*, Vol. 20, pgs. 42-48, 2002 (Liu), and Ming *et al.*, *Pharmacology Reviews* 2002, of record cited in the IDS filed 9/22/09 (Ming).

In support of this rejection, the Examiner states that Sasaki teaches a compound comprising a DNA polynucleotide and a carrier comprising a mannan molecule, wherein the polynucleotide is in the "claimed range" (presumably referring to the range claimed in claims 52 and 53). As mentioned above, the Examiner agrees that Sasaki does not teach a "carrier comprising a plurality of aldehydes" (as presently claimed in claims 59-61). However, the Examiner then argues that it would have been obvious to "oxidize the mannan and use in a complex comprising the DNA vaccine given that Apostolopoulos teach[es that] the presence of the additional aldehyde groups allow for more efficient entry into the cytoplasm of the cell and mediation of the immune response".

Apostolopoulos is entirely directed to teaching that oxidized mannan, compared to reduced mannan, is associated with "rapid and efficient MHC Class 1 presentation to CD8+ cells and a preferential T1 response"; whereas "after reduction there is class II presentation and a T2 response" (see, for example, the abstract). Particularly, Applicants note that Apostolopoulos does *not* at all disclose or suggest that oxidised mannan influences the efficiency of internalization. In fact, at page 1720, right column, Applicants submit that Apostolopoulos actually teaches away from this concept, stating that "[i]n this study, it was apparent that both oxidized (*and reduced*) mannan bind to the MR and are internalized in the same way as other mannose-containing entities … the selective advantages of oxidized material occurred *after* the binding/internalization step" (*emphasis added*).

Further, the conjugate of Apostolopoulos is entirely directed to an oxidised mannan molecule bound to a *protein antigen* (MUC-1) rather than a *polynucleotide or oligonucleotide*. Applicants consider that this is a critical difference between Apostolopoulos and the present invention, as the person skilled in the art would expect that an internalised protein antigen would be readily directed to the MHC Class I and Class II pathways as disclosed in Apostolopoulos, and therefore "mediate an immune response." However, a person skilled in the art reading Apostolopoulos, would not expect that a conjugate of the present invention (comprising a polynucleotide or oligonucleotide molecule instead of a protein antigen) would have *any* influence on the immune response due to the MHC Class I or Class II pathways, as a person skilled in the art would not consider that a nucleotide or oligonucleotide molecule would enter these pathways. Accordingly, Apostolopoulos does not at all (1) disclose or suggest that oxidised mannan provides any benefit, compared to reduced mannan, at achieving internalisation of a conjugate, or (2) provide any disclosure or even suggestion that a polynucleotide or oligonucleotide conjugated to oxidised mannan preferentially would affect the immune response. Thus, the person skilled in the art having read Sasaki and Apostolopoulos would not be motivated to try testing a conjugate comprising *a polynucleotide or oligonucleotide molecule* and a carrier comprising *at least one aldehyde group*.

Turning to Liu, this document discloses a topically applied HIV DNA vaccine (comprising expression plasmids encoding HIV antigens) that is co-administered with expression plasmids encoding cytokines (noting that the plasmids are *not* conjugated to one another). The document discloses that the *cytokine* expressing plasmids (when co-administered with HIV vaccine) induced a stronger immune response to vaccination.

Bearing in mind that Liu does not disclose or suggest the use of any *conjugate* comprising one or both of the expression plasmids, it is difficult to see how this document is relevant to the present invention. However, in this regard, the Examiner has argued that "one would have further combined an *antigen* into said complex to enhance the immune response more efficiently as taught by Liu et al." Applicants presume that the Examiner intended to refer to "a polynucleotide or oligonucleotide encoding an antigen", given that neither the conjugate of the present invention nor the DNA vaccine of Liu includes a protein antigen. However, noting that the presence of the "antigen" of Liu (unsurprisingly) did enhance the immune response compared to "empty" plasmids (see, for example, Table 1), Applicants consider that Liu nevertheless does nothing to render obvious the present inventive finding that conjugation of a polynucleotide or oligonucleotide molecule to a carrier comprising at least one aldehyde group can be used to achieve cell delivery of the polynucleotide or oligonucleotide molecule in a manner to enable, in one embodiment wherein the molecule encodes an antigen, a primarily CD8+ type immune response (see, for example, page 4 lines 7 to 15) or, at higher dosage, a strong CD8+ type immune response and a strong CD4+ type immune response. As mentioned at page 10, the Applicants believe that the successful cell delivery of the polynucleotide or oligonucleotide molecule using the conjugate of the present invention is achieved through the action of the at least one aldehyde group to prevent degradation of the polynucleotide or oligonucleotide molecule upon endocytosis bringing about the release of the polynucleotide or oligonucleotide molecule from the formed endosome into the cytoplasm before the endosome fuses with a lysosome containing degradative enzymes. There is nothing in the combined disclosure of Sasaki, Apostolopoulos, or Liu. to allow a person skilled in the art to suspect or predict that this may be the effect of including at least one aldehyde group on a suitable carrier conjugated to a polynucleotide or oligonucleotide molecule.

With regard to Ming, this document is directed to drug delivery via the transferrin pathway, and discloses (amongst other things) transferrin-poly-lysine-DNA conjugates (see, for example left column of page 575 to the left column of page 577). The Examiner has argued that in the light of this disclosure, "it would have been obvious to use a polycation linker for conjugations." As such, it appears that Ming is only relevant to claims 67 and 68. However, Ming, standing alone, is not sufficient to render obvious the broader, present claim 50, and for the reasons given above, the invention is not obvious over Sasaki in view of Apostopoulous and Liu. Accordingly, Applicants respectfully request that the examiner withdraw the rejection of claims 50, 52-55, and 59-69 as obvious over Sasaki in view of Apostolopoulos, Liu, and Ming.

Claims 50, 51 and 58-61 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Azzam *et al.*, *Macromol Symp.* 2003 of record cited on International Search Report filed 5/12/2006 (Azzam), and U.S. Patent Publication No. 2004/0259247 (Tuschi).

In support of this rejection, the Examiner argues that Azzam discloses the use of an *oxidized* dextran carrier. However, in making this argument, the Examiner has overlooked that the process disclosed by Azzam involves oxidizing dextran to obtain polyaldehydes, which are then *reduced,* thereby removing the aldehyde groups from the carrier. Specifically (as outlined in the Abstract; at pages 250-251 in sections 2.2, 2.3 and 2.4; and at page 252 in section 3.1), dextran was oxidized with potassium perioxidate and converted to a dextran-oligoamine *conjugated* by *reduction*, particularly by the addition of excess sodium borohydride for 48 hours, *prior to conjugation with DNA.* This *reduction reaction then was repeated* (prior to conjugation with DNA), presumably to *ensure* the dextran-oligoamine complex was fully reduced. Finally, the dextran-oligoamine complex was then conjugated to DNA. Accordingly, Applicants do not consider that Azzam teaches a conjugate comprising a carrier with an at least one aldehyde group conjugated to a polynucleotide or oligonucleotide molecule, and in fact, teaches away from the present invention.

Tuschl is directed to double stranded RNA molecules that are capable of mediating RNA interference. The Examiner asserts that it would have been obvious to conjugate the carrier of Azzam. to deliver double stranded RNA as taught by Tuschl to cells. However, neither of these documents teaches a conjugate comprising a carrier comprising at least one aldehyde group. Accordingly, Applicants respectfully request that the examiner withdraw the rejection of claims 50, 51, and 58-61 as obvious over Azzam and Tuschl.

Conclusion

In view of the above, all objections and rejections have been sufficiently addressed. The Applicants submit that the application is now in condition for allowance and request that claims 50-55 and 58-69 be allowed and this application passed to issue.

In the event that this paper is not timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By: / Barbara G. Ernst /
Barbara G. Ernst
Attorney for the Applicant
Reg. No. 30,377
ROTHWELL, FIGG, ERNST & MANBECK
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
(202) 783-6040